

A Comparison of the Nicotine Lozenge and Nicotine Gum: An Effectiveness Randomized Controlled Trial

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ABSTRACT

Context: Both the nicotine gum and nicotine lozenge have been shown to increase smoking cessation rates, but no published trials have directly compared the two. Higher dose nicotine gum has been recommended as a treatment that may reduce cessation-related weight gain.

Design/Outcome: In a diverse urban setting, 408 participants were randomized to receive either the lozenge or the gum for 8 weeks of treatment. Seven-day point prevalence of smoking abstinence was biochemically confirmed by exhaled carbon monoxide levels of less than 10 ppm measured at 8 weeks with follow-up at 6 and 12 months.

Results: At 8 weeks, the lozenge quit rate was 15.1% and the gum quit rate was 11.3%, with an odds ratio of 1.39, 95% confidence interval (0.78-2.49) $P=0.26$. These rates compare favorably to a historical spontaneous quit rate of 5%. Quit rate comparisons were similarly non-significant at 6 and 12 months. At 8 weeks, successful quitters in the lozenge group gained 3.0 ± 6.3 lbs compared to the gum group, which gained 8.4 ± 9.2 lbs with $t=-2.4$, $P=0.02$, but this finding was not sustained at 6 and 12 months.

Conclusions: The gum and lozenge appear equally effective for smoking cessation; however, for patients concerned about preventing cessation related to immediate weight gain, the lozenge may be the better agent.

INTRODUCTION

Tobacco use is the number 1 cause of overall preventable mortality in the United States, accounting for approximately 440,000 deaths each year.¹ Despite public health efforts to decrease tobacco use, 21% of the adult population still smokes.² Of these, 70% would like to quit, and 42.5% of smokers make a quit attempt each year.² The quit rate for those utilizing no form of treatment is approximately 5% per year, making the need to increase smoking cessation rates a top public health priority.³

Nicotine replacement therapy (NRT) has been shown to increase smoking cessation rates, relative to placebo. Both the nicotine gum and nicotine lozenge are US Food and Drug Administration (FDA) approved and have been shown to increase a smoker's chance of successfully quitting, with meta-analysis odds ratios (OR) of 1.66 (95% confidence interval [CI]: 1.52 to 1.81) and 2.05 (95% CI: 1.62 to 2.59) respectively.⁴ The gum's efficacy is well established, but to date only 1 randomized controlled efficacy trial on the lozenge has been published.⁵ In this trial, the lozenge showed efficacy among light smokers, heavy smokers, and smokers who had previously failed pharmacotherapy.⁶⁻⁷ The lozenge is generally well tolerated, has a similar side effect profile to nicotine gum (mouth irritation, nausea, heartburn, hiccups, etc) without requiring a special technique for optimal use (park and chew).⁸ It also delivers more nicotine than the equivalent dose of the gum.⁹ These features suggest the lozenge may be a more effective method of oral nicotine replacement. The results of the single randomized controlled trial on the lozenge support this conjecture as the lozenge produced impressive abstinence rates at 6-month follow-up.⁶

In addition to examining the relative efficacy of these 2 pharmacotherapies, we also examined variables that might make these medications more or less appealing to smokers. Specifically, we examined weight gain and adverse events. Weight gain is a common and vexing side effect of smoking cessation. In the first year

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after successfully quitting smoking, most patients typically gain 10-14 pounds.¹⁰ Weight gain concerns are a significant barrier to some smokers.¹¹ Both the gum and the lozenge have been shown to delay, but not prevent, weight gain.^{6,11} Nicotine gum in higher doses appears to reduce cessation-related weight gain¹² and has been recommended as a strategy to prevent it.

In addition, effectiveness of self-administered NRT appears to be more modest in “real world” effectiveness trials than in efficacy trials.¹³ Thus, there is clear need to examine the performance of the nicotine lozenge in the effectiveness context as the existing efficacy trials may produce a relatively high estimate of clinic impact.

No trials directly comparing the nicotine lozenge and gum have been published to date. Lack of such information leaves patients and clinicians with little direction in choosing between the 2 treatments. Both are available over-the-counter and have the potential for widespread ad-lib use. Their cost per day is modest and can be less expensive than a pack of cigarettes. We therefore set out to compare the nicotine lozenge and gum in a direct “head to head” trial measuring quit rates, side effect profiles, and cessation-related weight gain in an urban setting with minimal controls, instructions, or reinforcements.

METHODS

Design

The study was conducted at the Aurora Sinai Medical Center in Milwaukee, Wis between June 2004 and July 2005. The present study was an effectiveness study with a 2 (medication conditions) x 2 (psychosocial interventions) design. Participants were randomized to receive either the nicotine lozenge or nicotine gum. They were also randomized to receive either 4 calls from the Wisconsin Tobacco Quit Line or a self-help brochure. Participants were treated with 8 weeks of NRT. Follow-up occurred at 8 weeks, 6 months, and 1-year post cessation attempt. Written informed consent was obtained from all participants and the University of Wisconsin Health Sciences Institutional Review Board approved consent forms and procedures. The study was conducted in compliance with ethical principles of the Declaration of Helsinki and the standards of good clinical practice developed by the International Conferences on Harmonization.

Screening and Eligibility

Participants were recruited by press release, newspaper and radio ads, flyers, and word of mouth to join the study. Men and women who were 18 years of age or older, smoked ≥ 10 cigarettes per day for the past 6

months, wanted to quit, had exhaled carbon monoxide (CO) levels of ≥ 10 ppm, had reliable access to a telephone, and planned to reside in the area for the next 12 months were eligible for enrollment. All interested participants were pre-screened by phone, and eligible participants made a clinic visit, at which, if they qualified for inclusion, they were immediately randomized to 1 of the 4 conditions previously mentioned.

A participant was considered ineligible if they were currently using another smoking cessation medication (ie, other forms of NRT, bupropion [Wellbutrin™, Zyban™]), had contraindication to the use of nicotine gum or nicotine lozenge (temporal mandibular joint disease, or other dental disease that would prevent safe gum chewing), had recent unstable cardiovascular disease (myocardial infarction, heart attack, or irregular heart beat/rhythm in the past 2 weeks), or had significant mental illness that would place the participant at risk (active depression with suicidality, or active psychotic symptoms). If female and premenopausal, the participant could not be pregnant and had to agree to use an effective birth control method during the treatment period.

Procedure

At randomization, baseline measurements were taken and included height, weight, demographics, smoking history, baseline carbon monoxide (CO) level, concurrent medications, and the Fägerstom Test of Nicotine Dependence questionnaire.¹⁴ Randomization was done in 13 blocks of 36 participants, blocked by gender. Gender was used as a blocking variable because of hypothesized gender differences in response to nicotine replacement therapy.¹⁵ Participants were given a 4-week supply of either nicotine gum or nicotine lozenge with instructions for use. At 4 weeks post-quit, participants could request additional medications for weeks 5-8 if desired.

If patients were randomized to the Wisconsin Tobacco Quit Line group, a baseline call to the Quit Line was made at the time of the initial enrollment, while in the office. During that phone call, cessation counseling was provided, and plans for future phone contacts were made. Specifically, plans were made for 3 follow-up calls: 1 call on or within 1-2 days of the Target Quit Date (TQD), a second phone call within 7-10 days of the TQD, and a third phone call within the next 30 days following the TQD. Patients could proactively call the Quit Line if desired; this was neither encouraged nor discouraged.

All participants were assessed via phone at 1 week post-TQD. Smoking status by self-report was assessed.

Table 1. Characteristics of Participants

	Quit Line and Lozenge	Quit Line and Gum	Self Help and Lozenge	Self Help and Gum
Number of participants	104	101	101	102
Average age in years (SD)	43.4 (12.7)	40.0 (12.0)	43.2 (13.1)	43.6 (10.9)
Men (% of participants)	45 (43.2)	45 (44.6)	45 (44.6)	44 (43.1)
Race (% of participants)				
White	75 (72.8)	65 (68.4)	65 (67.0)	74 (76.3)
Black	28 (27.2)	24 (25.3)	29 (29.9)	21 (21.6)
American Indian	0 (0)	2 (2.1)	0 (0)	1 (1.0)
Asian	0 (0)	0 (0)	1 (1.0)	0 (0.0)
Other	1 (1.0)	10 (9.9)	6 (5.9)	6 (5.9)
Number of years smoked (SD)	26.5 (12.2)	23.5 (11.6)	26.0 (12.6)	27.1 (11.2)
Average number of cigarettes per day in last month (SD)	23.8 (10.2)	22.3 (9.8)	23.3 (9.9)	22.9 (9.6)
Average Fagerstrom Test for Nicotine Dependence score (SD)	5.9 (2.2)	5.7 (2.3)	6.2 (2.1)	6.1 (2.1)
Number of prior quit attempts	3.4 (2.5)	4.2 (5.0)	4.4 (3.8)	3.9 (3.4)

SD=standard deviation

No counseling or advice was given during that or any other follow-up phone calls from the research center. At 8 weeks post-TQD, all participants attended a clinic visit. Smoking status, exhaled CO levels, adverse events, medication usage, and height and weight were assessed. Participants could request 4 additional weeks of NRT for tapering purposes if they desired, regardless of smoking status.

Further follow-up occurred by telephone at 6 months post-TQD and 12 months post-TQD. Only those who reported abstinence were invited for in-person clinic visits, at which time smoking status was confirmed with exhaled CO measurement and height and weight were measured.

Outcome Measures

The primary outcome measurement was 7-day point prevalent abstinence confirmed with exhaled CO of <10 ppm at 8 weeks post-TQD. Secondary outcomes were CO confirmed 7-day point prevalence at 6 and 12 months post-TQD as well as weight gain, and adverse events. Intensity of use of the Quit Line, use of NRT, gender, and race were used as variables for subgroup analysis. Participants lost to follow-up at any point were considered as relapsed and analyzed as continuing smokers using an intent-to-treat analysis.

Statistical Methods

All statistical tests were 2-sided with a Type I error rate of 0.05. Abstinence rates were expressed as binary data and were analyzed using a logistic regression model including main effects of treatment group.

A sample size of 100 participants per group was chosen to have 81% power to detect a difference between the lozenge versus gum assuming a 12% difference (29.5 for lozenge versus 17.5 for gum). Statistical significance

was tested by comparing each individual condition against every other and then collapsing across treatment dimensions. For all analyses, data were collapsed across the counseling dimension, since this did not interact with the NRT condition.

RESULTS

Randomization

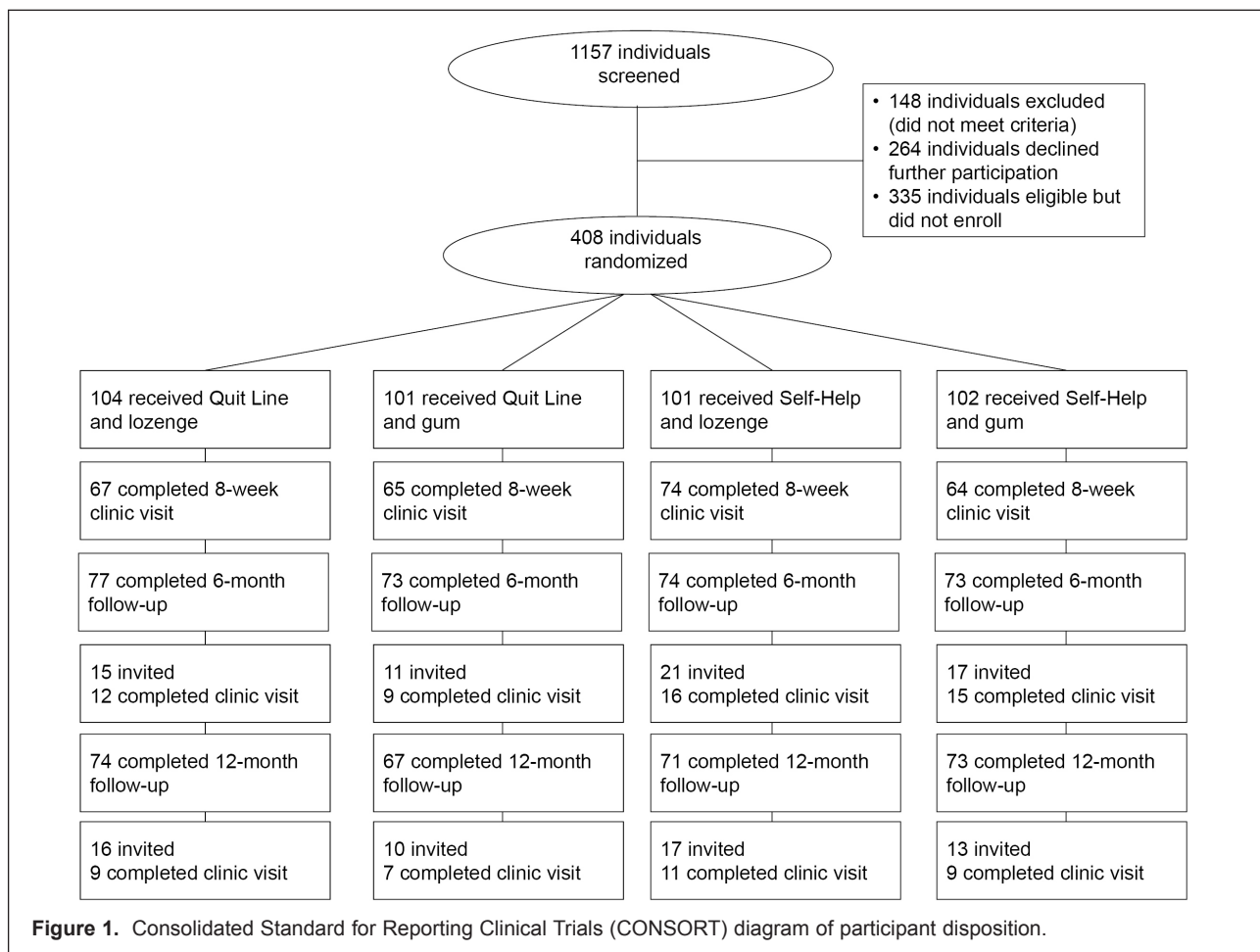
A total of 1155 people were screened for participation. One hundred forty-eight were excluded based on inclusion/exclusion criteria, 264 people declined further participation, and 335 were eligible, invited for a clinic visit, but never visited the clinic and were never enrolled into the study. Four hundred eight participants were randomized into 4 groups. Baseline characteristics are shown in Table 1. There were no significant baseline differences between groups.

Participant disposition is shown in Figure 1. Overall follow-up rates at 8 weeks, 6 months, and 12 months were 64.0%, 72.8%, and 69.9%, respectively, with little variation between groups. Of those reporting abstinence via phone follow-up who were subsequently invited for a clinic visit for CO confirmation at 6 and 12 months, 81.3% and 64.3% completed the clinic visit respectively, with little variation across the groups.

Participants were asked to return all unused NRT at the 8-week visit, but only approximately 60% of participants did so. Because of the limited response rate, NRT utilization estimates were considered unreliable enough to preclude further analyses.

Cessation Rates

To test the main effect of medication, we collapsed across the Quit Line and Self-Help conditions. It should be noted that there were no omnibus differ-



ences between counseling conditions and no interactions between groups. Results are shown in Table 2 and Figure 2. At 8 weeks, the lozenge quit rate was 15.1% and the gum quit rate was 11.3% with an OR of 1.39, 95% CI (0.78-2.49) $P=0.26$. At 6 months the OR was 1.24 (0.64-2.38) $P=0.53$. At 12 months the OR was 1.38 (0.67-2.83) $P=0.38$. Although slightly higher quit rates were observed at all time points among lozenge users, these differences were not statistically significant.

Because this effectiveness study was conducted with a diverse urban population, cessation rates were also examined for pre-defined demographic subpopulations. Among the 102 (25.0%) African Americans randomized, the overall quit rate across all conditions was 9.8% compared to the non-African American overall quit rate of 14.4% at 8 weeks, a non-significant difference. No difference was found between the lozenge and gum as a function of race.

Among the 223 (55.9%) women randomized, the overall quit rate was 11.7%, compared to men at 15.1%. This comparison was non-significant at all time points. However, among men, the lozenge trended toward

being more effective than the gum at all time points. At 8 weeks, 6 months, and 12 months the quit rate, comparison rate, and odds ratios (with CI) were 18.5% versus 11.8%, OR 1.69 (0.74-3.84), 14.1% versus 6.5% OR 2.39 (0.86-6.58), and 13.0% versus 4.3%, OR 3.33 (1.03-10.7) respectively, reaching marginal significance at 12 months. Small cell sizes did not permit analysis of gender and racial/ethnic interactions.

Weight Outcomes

Weight outcomes are shown in Table 3 by type of nicotine replacement therapy and smoking status. At 8 weeks, successful quitters in the lozenge group gained 3.0 ± 6.3 lbs compared to the gum group, which gained 8.4 ± 9.2 lbs with $t=-2.4$, $P=0.02$. At 6 months no statistical difference was found with weight gain 8.7 ± 11.6 versus 13.6 ± 9.7 , $t=-1.5$, $P=0.13$. At 12 months the difference was 6.3 ± 27.4 versus 13.5 ± 13.5 $t=-1.0$, $P=0.32$. Among participants who relapsed, weight gain was 0.9 lbs versus 1.8 lbs $t=-1.1$, $P=0.27$. At all time points, regardless of smoking status, the lozenge appeared to reduce weight gain compared to the gum, but this effect was only significant during the treatment phase among successful quitters.

Table 2. Seven-day Point Prevalence of CO-confirmed Abstinence for Lozenge vs Gum

Follow-up Period	Nicotine Lozenge n=205 (%)	Nicotine Gum n=203 (%)	OR (95% CI)	P value
8 weeks	31 (15.1)	23 (11.3)	1.39 (0.78-2.49)	0.26
6 months	22 (10.7)	18 (8.9)	1.24 (0.64-2.38)	0.53
12 months	19 (9.3)	14 (6.9)	1.38 (0.67-2.83)	0.38

OR=odds ratio; CI=confidence interval.

Side Effects/Adverse Events

Adverse Events are shown in Table 4. Total number of reported adverse events was 61 (43.3%) in the lozenge group and 42 (32.6%) in the gum group. The most common side effects were nausea, mouth/jaw/throat irritation, hiccups, and heartburn, with rates for the lozenge being 9.2, 8.5, 5.7, and 5.7 percent respectively. Rates for the gum were 6.2, 8.5, 3.1, and 0.8 percent respectively. Frequency of events was similar across groups with no statistical differences between the groups.

One death occurred 47 days after end of treatment and was determined to be from a post-operative complication following mitral valve replacement surgery and was not related to the study medication.

DISCUSSION

The study demonstrated a nonsignificant trend toward increased effectiveness of the lozenge for smoking cessation. Subgroup analysis suggests the effect may have reflected a superior response among men. As originally suggested by Perkins et al,¹⁵ a meta-analysis by Cepeda-Benito et al¹⁶ found that among trials using all types of NRT compared to placebo, men had superior cessation rates over women at all time points but only reached statistical significance at 12-month follow-up. They concluded that NRT is more effective for men, and that women need more nonpharmacologic support to maintain abstinence long term. One critique of this theory was the discovery of a possible reporting bias, meaning that, when reviewing the literature for meta-analysis, only studies with positive gender associations were reported and published, while other trials with negative or insignificant associations never reported gender data. In addition, a meta-analysis by Munafo et al,¹⁷ published essentially simultaneously with Cepeda-Benito's meta-analysis, found no meaningful differences in NRT response rates at all times points between men and women among trials of the nicotine patch compared to placebo. As a result, the issue remains unresolved.¹⁸ We demonstrated a trend toward more effectiveness in men with the lozenge, but failed to find reliable statistical differences. Presumably, the lozenge might produce

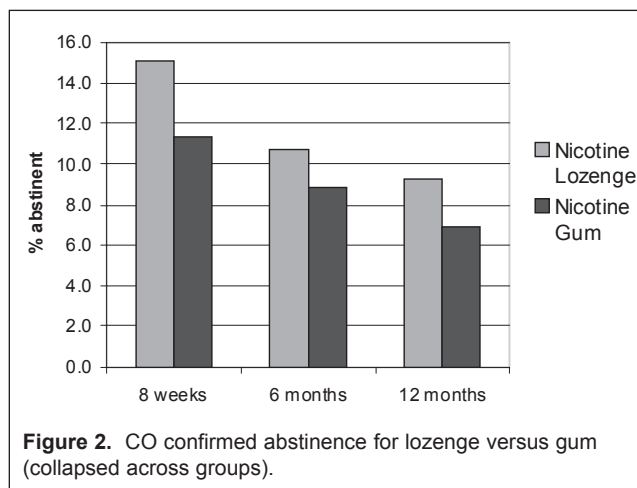


Figure 2. CO confirmed abstinence for lozenge versus gum (collapsed across groups).

superior effects in men due to a higher delivered nicotine dose.

The statistically significant finding in this “real world” effectiveness study was the difference in weight gain among users of the lozenge compared to the gum. On average, those using the lozenge experienced 5.4 fewer pounds of post-cessation weight gain at 8 weeks. On average, all abstinent participants gained weight, but those in the lozenge group gained less weight. This effect also could reflect the more efficient nicotine delivery of the lozenge, compared to nicotine gum.⁹ In addition, the side effect profiles of the gum and lozenge were quite similar, suggesting that either is a safe treatment option. As this study represents the first direct comparison of these 2 NRTs in an effectiveness trial, the results indicate that both therapies are similarly effective for cessation, but that the lozenge may confer significant benefit in terms of delaying post-cessation weight gain.

There are strengths and weaknesses to an effectiveness design. Notably, there was no placebo group in this study, so comparisons to an internal reference could not be made. However, both the lozenge and gum in this study compare favorably to unaided quit rates.^{10,19} Due to the limited return of medication at week 8, it was not possible to reliably estimate gum or lozenge usage and the potential impact of rate of use on cessation. This occurred because participants were asked only once at randomization to return unused NRT at

Table 3. Weight Gain by Type of NRT and Smoking Status

	Lozenge group pounds gained (SD)	Gum group pounds gained (SD)	t value	P value
Abstinent				
8 weeks	3.0 (6.3)	8.4 (9.2)	-2.4	0.02
6 months	8.7 (11.6)	13.9 (9.7)	-1.5	0.13
12 months	6.3 (27.4)	13.6 (13.6)	-1.0	0.32
Relapsed				
8 weeks	0.9 (7.1)	1.8 (5.0)	-1.1	0.27

NRT=nicotine replacement therapy

Table 4. Reported Adverse Events

	Nicotine lozenge group n=141 (%)	Nicotine gum group n=129 (%)
Nausea ^a	13 (9.3)	8 (6.2)
Mouth irritation ^b	12 (8.5)	11 (8.5)
Heartburn ^c	8 (5.7)	4 (3.1)
Hiccups	8 (5.7)	1 (0.8)
Other adverse events	20 (14.2)	18 (14)
Total	61 (43.3)	42 (32.6)

^a Nausea, stomach upset, stomach pain

^b Mouth irritation, burning mouth, mouth sores, sore gums, jaw pain, dry mouth

^c Heartburn, GERD, reflux

the 8-week clinic visit and many participants forgot. No other reminders were given and no aggressive NRT usage tracking was done, in keeping with the effectiveness study design. Since rates of use with ad lib NRTs may have a significant impact on success rates, this is a significant limitation compared to a highly-controlled efficacy study where rates of NRT use are typically tracked with more precision and are typically known in 90%-98% of participants.⁵ Strengths of the study are that 25% of the population was African American and the education levels and socioeconomic status were diverse. Thus, the results may be generalizable to the current population of smokers, since smoking is becoming increasingly concentrated in low SES populations.²⁰ In addition, follow-up was consistent across all groups in the study, increasing confidence that the observed findings are reliable.

CONCLUSIONS

This effectiveness study, conducted with a diverse urban population, identified a significant benefit of the nicotine lozenge in reducing post-cessation weight gain relative to nicotine gum. It suggested a possible differential cessation benefit for male smokers, but this result was not consis-

tently significant and would require replication. Further research is needed to clarify the optimal agent for smoking cessation in general populations of smokers.

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